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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,150	09/10/2001	Kenneth J. Livak	9584-018	9176

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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,150	LIVAK ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e)(d) based upon a United States provisional application filed on March 27, 2000. A claim for priority under 35 U.S.C. 119(e) cannot be based on said application, since the current United States application was filed more than twelve months thereafter.

Claim Rejections - 35 USC § 112

1. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Method claims require some step or phrase that states or functions to achieve the accomplishment of the goals for the method which were stated in the method's preamble. Claims 1-13 lack such a last step and are confusing because the additional method steps are not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986).

In particular, the final step of "determining whether the signal exhibits a specific behavior as a function of time" is not connected to the method of detecting a target polynucleotide. While the specification discusses (for example at page 3) that some signals can be differentiated from background based upon their behavior as a function of time, the final step does not correlate this behavior with the step of detection, which is

the essential method indicated by the preamble. Therefore the claim is indefinite. A step correlating the detection of the target nucleic acid molecules with the specific behavior would obviate this rejection.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-3 and 8-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Ryan et al (Molecular Diagnostics (June 1999) 4(2):135-144).

Ryan teaches a method of detecting a target polynucleotide (abstract) which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another (see page 137, figure 1, molecule labeled "primary target molecule" with: (i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide (see page 137, figure 1, molecule labeled "primary invader oligonucleotide") ; (ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the

second portion of the target polynucleotide and a flap region located adjacent to the first region (see page 137, figure 1, molecule labeled "primary probe oligo"); and (iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide (see page 137, figure 1, "cleavage by cleavase VIII enzyme");

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected (see page 137, figure 1, "secondary invader reaction");

(b) detecting the reporter to provide a signal (see page 137, figure 1 and page 139, columns 1 and 2); and

(c) determining whether the signal exhibits a specific behavior as a function of time (see page 139, columns 1 and 2, here the time function is found in the basic control. That is, the control with no DNA target represents a time function of zero with regard to the completed reaction since the reaction cannot start while the actual value determined represents a time value of completed reaction. This relies upon a broad interpretation of the phrase "specific behavior as a function of time" in the claim and no definition limiting this phrase was found in the specification).

Ryan further teaches the limitations of claims 2 and 3, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases

can have multiple regions) a first region and a second "flap" region which hybridizes to the target polynucleotide (see page 137, figure 1).

Ryan further teaches the limitations of claim 8-9 where the second portion is located immediately 3' to the first region (see page 137, figure 1, "primary target molecule") and where the "flap" of the invader is 3' to the region and the flap of the probe is 5' to the probe (see page 137, figure 1 where the "flap" of the invader can interact with the target molecule and is therefore inherently present as part of the invader oligo).

Ryan teaches the limitation of claim 10 that the method is fluorescent signal detection (see page 137, figure 1, signal detection with fluorescent plate reader).

4. Claims 1-3 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Lyamichev et al (Nature Biotechnology (March 1999) 17:292-296)

Lyamichev teaches a method of detecting a target polynucleotide (abstract) which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another (see page 293, figure 1) with: (i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide (see page 293, figure 1); (ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and a flap region located adjacent to the first region (see page 293, figure 1); and (iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second

portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide (see page 293, figure 1, Fen endonuclease cleavage);

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected (see page 294, figure 4);

(b) detecting the reporter to provide a signal (see page 294, figure 4); and

(c) determining whether the signal exhibits a specific behavior as a function of time (see page 294, figures 4 and 5, here the time function is found in the basic control. That is, the control with no DNA target represents a time function of zero with regard to the completed reaction since the reaction cannot start while the actual value determined represents a time value of completed reaction. This relies upon a broad interpretation of the phrase "specific behavior as a function of time" in the claim and no definition limiting this phrase was found in the specification).

Lyamichev further teaches the limitations of claims 2 and 3, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which hybridizes to the target polynucleotide (see page 293, figure 1, panels A and C).

Lyamichev further teaches the limitations of claim 8-9 where the second portion is located immediately 3' to the first region (see page 293, figure 1) and where the "flap" of the invader is 3' to the region and the flap of the probe is 5' to the probe (see page

293, figure 1 where the "flap" of the invader can interact with the target molecule and is therefore inherently present as part of the invader oligo).

Lyamichev teaches the limitation of claim 10 that the method is fluorescent signal detection (see page 294, figure 4, signal detection with fluorescent detection).

5. Claims 1-5 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hall et al (U.S. Patent 5,994,069).

Hall teaches a method of detecting a target polynucleotide (see column 37) which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another (see column 37, lines 34-36 and figure 25) with: (i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide (see column 37, lines 41-47 and figure 25); (ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and a flap region located adjacent to the first region (see column 37, lines 37-40 and figure 25); and (iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide (see column 37, line 33 and figure 25);

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region

of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected (see column 37, figure 25);

(b) detecting the reporter to provide a signal (see column 8, lines 39-67); and

(c) determining whether the signal exhibits a specific behavior as a function of time (see figure 100, which shows a time course, here the time function is found in the basic control. That is, the control with no DNA target represents a time function of zero with regard to the completed reaction since the reaction cannot start while the actual value determined represents a time value of completed reaction. This relies upon a broad interpretation of the phrase "specific behavior as a function of time" in the claim and no definition limiting this phrase was found in the specification).

Hall further teaches the limitations of claims 2 and 3, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which hybridizes to the target polynucleotide (see column 37, lines 30-40 and figure 25).

Hall further teaches the limitations of claims 4 and 5, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which does not hybridize to the target polynucleotide (see column 38, lines 1-12 and figure 28, panel C).

Hall further teaches the limitations of claim 8-9 where the second portion is located immediately 3' to the first region (see figure 25) and where the "flap" of the invader is 3' to the region and the flap of the probe is 5' to the probe (see figure 25).

Hall teaches the limitation of claim 10 that the method is fluorescent signal detection (see column 8, lines 39-67, signal detection with fluorescent detection).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al (U.S. Patent 5,994,069) as applied to claims 1-5 and 8-10 in view of

Hall teaches a method of detecting a target polynucleotide (see column 37) which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another (see column 37, lines 34-36 and figure 25) with: (i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide (see column 37, lines 41-47 and figure 25); (ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and a flap region located adjacent to the first region (see column 37, lines 37-40 and figure 25); and (iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide (see column 37, line 33 and figure 25);

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected (see column 37, figure 25);

(b) detecting the reporter to provide a signal (see column 8, lines 39-67); and

(c) determining whether the signal exhibits a specific behavior as a function of time (see figure 100, which shows a time course, here the time function is found in the basic control. That is, the control with no DNA target represents a time function of zero with regard to the completed reaction since the reaction cannot start while the actual value determined represents a time value of completed reaction. This relies upon a

broad interpretation of the phrase "specific behavior as a function of time" in the claim and no definition limiting this phrase was found in the specification).

Hall further teaches the limitations of claims 2 and 3, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which hybridizes to the target polynucleotide (see column 37, lines 30-40 and figure 25).

Hall further teaches the limitations of claims 4 and 5, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which does not hybridize to the target polynucleotide (see column 38, lines 1-12 and figure 28, panel C).

Hall further teaches the limitations of claim 8-9 where the second portion is located immediately 3' to the first region (see figure 25) and where the "flap" of the invader is 3' to the region and the flap of the probe is 5' to the probe (see figure 25).

Hall teaches the limitation of claim 10 that the method is fluorescent signal detection (see column 8, lines 39-67, signal detection with fluorescent detection).

While Hall expressly recognizes background as a problem, noting "Background cleavage due to thermal breakdown of probe oligonucleotides can, when not resolved from specific cleavage products, reduce the accuracy of quantitation of target nucleic acids based on the amount of accumulated product in a set timeframe. (see column 54,

lines 46-50), Hall does not teach modes of data analysis to overcome this issue of undesired background.

Wittwer, as per claim 11, teaches solving the problem of background fluorescence by real time analysis of the signal as a function of time (see figure 2 and column 6) including on exonuclease type assays (see column 6, line 46). Wittwer expressly teaches, as relates to claims 6 and 7, non-linear behavior, which is quadratic, for the specific signal as shown by the curve in figure 5, where the linear fluorescence result is shown as negative and the curve is shown as positive. Wittwer provides the analytical framework for this analysis in column 7, especially lines 5-45. As in claims 12 and 13, Wittwer discusses measuring the signal at a plurality of times to provide a data set as shown in figures 2 and 5, where sequential times or cycles are measured, fitting the data to a polynomial function comprising a linear and quadratic term, here the derivatives (See column 7, line 57 to column 8, line 67), and determining whether the coefficient is greater than zero (column 8, lines 63-67). In particular, Wittwer is transforming the signal to a new domain, here the algorithm disclosed and comparing the shapes of the mathematical functions to determine whether the signal is positive or negative (see column 8 and figure 5, which shows a linear versus quadratic curve as negative versus positive for detection).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to solve the background problem of Hall using the

methodology of Wittwer since Wittwer states that by use of his method the analytical "process is automated so that a user can prepare a biological sample and simply place it in a thermal cycler having a sensor for reporting fluorescence values as a function of cycle number and a processor programmed with an algorithm capable of processing the values and reporting a positive or negative result (see column 2, lines 53-58)". An ordinary practitioner would have been motivated to subject the method of Hall to the analytical method of Wittwer for the advantage of an automatic and rapid analysis of background which would distinguish positive from negative results. Further motivation is provided when Wittwer notes that the method may be applied to any amplification system (see column 5, line 47) including exonuclease probe designs such as those of Hall (see column 6, line 46). Lastly, motivation is provided by Hall's recognition that background is a problem and Wittwer's solution of the problem of background using mathematical analyses of the shapes of the curves to distinguish the linear background from the exponential signal (see columns 7 and 8).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

April 3, 2003